REMARKS

First, applicants truly appreciate the willingness of the Examiner to examine a somewhat different invention from that originally elected in the context of this RCE. This is extremely helpful and the Examiner is thanked for this consideration.

There are only two bases for rejection, both based on 35 U.S.C. § 103: Okabe, *et al., FEBS Lett* (1997) 467:313-319 in view of Kern (WO02/28188) and further in view of Yang, *et al., PNAS* (2002) 99:3824-3829. The second is made over Okabe in view of Kern and further in view of Verkhusha, *et al., J. Biol. Chem.* (2001) 276:29621-29624. These supersede the previous rejections made over Kern in view of Okabe.

Since Kern and Okabe are common to both rejections currently pending, these will be discussed first.

The Office cites Okabe for describing a "green mouse" which expresses green fluorescent protein in all of its cells except hair and erythrocytes. This mouse is made by inserting a transgene into fertilized eggs. Various lines were obtained of such green mice. However, as the Office recognizes, these mice are not immunocompromised.

This is asserted to be remedied by Kern who reportedly describes mice that at least in some tissues express green fluorescent protein and are immunocompromised. The description of Kern's mice is found on pages 10-11. Kern does not describe the four steps required in the present claim. These steps are required in order to establish a stable line of immunocompromised rodents that produce a florescent protein in all their tissues under constitutive promoter. Indeed, on page 10 in the description of forming these mice, Kern alludes to an inducible promoter. Applicants understand that on page 4, line 24, constitutive promoters were mentioned in the alternative, but it is not clear

and not expressly stated that these promoters provide expression in all tissues, as is the case in the present claims.

In any event, Kern fails to establish stable lines of rodents having the characteristics set forth in the claims, which applicants achieve by virtue of the claimed process used to prepare them, because Kern has no need for such stability. The only purpose for such mice noted by Kern is to provide labeling for endogenous cells so that tumor cells that are implanted into the immunocompromised host can be freed of contaminating host cells, in the case of florescent protein presumably by visual observation. There is no assertion in Kern, of course, that all of the tissues are constitutively labeled, since Kern has no need for this. And there is no suggestion in Kern that the mice that are immunocompromised and thus prepared should be models of tumor progression; they are simply hosts for tumor tissue which can be certified free of host tissue by virtue of labeling said host cells. The transgenic immunodeficient GFP mouse prophetically described by Kern is necessary only to facilitate purification of cells of interest; the mouse itself is not of interest.

Since the mouse is not of interest, one skilled in the art would not find it obvious or be motivated to combine the teachings of Okabe *et al.* which describes a purposeful biological use of a transgenic *non*-immunocompromised GFP mouse with the teachings of Kern that regards transgenic GFP immunocompromised mouse-derived cells as mere contaminants.

The Office notes that Okabe mentions using green mice by implanting them with non-green tumor cells. It is not clear how this could be even possible unless the mice were either immuno-compromised or synergeneic tumors were used. It is also not clear, as the Office kindly recognizes, how this model would be used and why the green background would be in any way helpful in

connection with the final requirement of the claim wherein the rodent is further modified to contain the tumor that produces a second florescent protein emitting at different wavelength from the first.

That said, it is evident that both rejections must fail unless the combination of Okabe and Kern with the tertiary documents is valid and defeating of patentability. As a preliminary remark, applicants acknowledge that it was known to be possible to perform dual imaging to determine the intensity of red and green fluorescent proteins, for example, at the same time. That is not at issue. At issue is whether the documents of record suggest preparing a rodent model in which a tumor of a different fluorescent wavelength will be followed in the context of a completely fluorescent rodent and result in enhanced ability to monitor tumor progression and progression of metastases from that tumor.

Yang clearly does not make this suggestion; in fact at some level, Yang could be considered to teach away from the present invention because the circumstances of the dual color imaging are so different. The only instance in the Yang paper of dual color imaging is separately implanting a green tumor and a red tumor at side-by-side locations in a mouse that has not been modified other than by being immunocompromised. There is nothing in Yang that would suggest providing a green mouse, for example, as a backdrop to a red tumor. It is not seen how injecting a green tumor and a red tumor into the same mouse would result in this suggestion, even when combined with Okabe and Kern. In Yang, the green and red fluorescent tumors are viewed separately, not a red tumor against a green background. And this is highly successful, as illustrated in Yang, et al., *Cancer Res* (2004) 64:8651-8656 of record.

Similar discussion applies to the rejection in combination with Verkhusha. Verkhusha's work appears at best to be irrelevant to the present invention. The Verkhusha paper is concerned

with a mutant red florescent protein that takes longer to exhibit its florescence upon illumination than green florescent protein. This is then used as a method to judge the maturity of cells – *i.e.*, cells are modified to contain expression systems for both a green fluorescent protein and the mutant red fluorescent protein. Cells thus modified will look green when they are younger and will look red when they are older. In the Verkhusha, publication, the same cells (not different types of cells) were transformed to express both proteins and the age of the cell judged by whether red or green florescence was exhibited. The cells in question were in *Drosophila*, an entirely different system from the rodent of the present invention.

In view of these major differences, it does not appear that Verkhusha is properly combined with Kern and Okabe, as it is concerned with red and green florescent protein in an entirely different context and not suggestive of, or predictive of the probable success of, the claimed rodent model.

Summary

For the reasons set forth above, applicants believe that the combination of Okabe and Kern does not render obvious even those aspects of the claim independent of the presence of the tumor that fluoresces at a different wavelength. In order to defeat patentability of the claim, however, the disclosures of the tertiary references must be combinable with those of Okabe and Kern to provide a suggestion of the invention as claimed. They fail to do this because Yang and Verkhusha do not relate to the present invention at all. Yang is concerned with two tumors of different colors being observed in a mouse lacking any fluorescent background and Verkhusha is concerned with production of both red and green fluorescent proteins in the same cell in order to assess the age of the cell in *Drosophila*.

Thus, claims 1-3 should be in a position for allowance and passage of these claims to issue as respectfully requested.

Should minor issues remain that could be resolved by telephone, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762004400.

Respectfully submitted,

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